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The M694I/M694I genotype: A genetic risk factor of AA-amyloidosis in a group of Algerian patients with familial Mediterranean fever

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ABSTRACT

Familial Mediterranean fever (FMF, OMIM 249100) is the most common hereditary fever, resulting from mutations in *MEFV*. FMF is characterized by episodic febrile attacks and polyserositis. Renal AA-amyloidosis is a major complication, which often leads to end-stage renal disease in untreated patients. The data about the renal AA-amyloidosis secondary to FMF are scarce in North African countries and non-existent in Algeria. We aimed to investigate the *MEFV* mutations associated with this complication in an Algerian patient cohort. Molecular analysis included 28 unrelated Algerian FMF patients with ascertained amyloidosis, 23 of them were symptomatic and 5 were asymptomatic. For this study, a group of 20 FMF patients without renal amyloidosis were selected as controls according to their age, disease onset and disease duration. The mutations were detected by sequencing exon 10 of *MEFV*. A total of 87.5% (49/56) mutant alleles were identified in 27/28 analyzed patients; p.M694I was predominant and appeared with an allele frequency of 62.5%, followed by p.M694V (17.85%), p.M680I (5.35%) and p.I692Del (1.78%). Remarkably, only p.M694I mutation was observed among the asymptomatic patients. The M694I/M694I genotype, identified in 14/27 (52%) patients, was significantly associated with the development of amyloidosis compared to group of controls ($p = 0.022$). This study did not link the M694V/M694V genotype to the renal complication despite the fact that it has been observed only in the patients with amyloidosis (3/27; 11%) ($p = 0.349$). The association of other identified genotypes to this complication was statistically insignificant. The progression of amyloidosis led to end-stage renal disease in 14 patients with 6 deaths. This study shows that p.M694I homozygosity is a potential genetic risk factor for the development of renal AA-amyloidosis in Algerian FMF patients.

1. Introduction

Familial Mediterranean fever (FMF, OMIM 249100) is an autosomal recessive disease that predominantly affects four ethnic groups, Arabs, Jews, Armenians and Turks (Ben-Chetrit and Touitou, 2009; El-Shanti et al., 2006). However, FMF is now recognized, world-wide to include populations with non-Mediterranean origin (Ben-Chetrit and Touitou, 2009). The first clinical symptoms of FMF appear in early childhood. The chronic relapsing inflammation of the serous membranes leads to febrile attacks often associated with abdominal, joint and chest pains (Ben-Chetrit and Levy, 1998; Shohat and Halpern, 2011). FMF is caused by mutations in the *MEFV* (MEditerranean FeVer) gene, located on chromosome 16p13.3 (French FMF Consortium, 1997; The International FMF

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Consortium, 1997). The most recurrent mutations, p.M680I, p.M694V, p.M694I and p.V726A are clustered in exon 10 of *MEFV* which encodes the B30.2 C-terminal domain of a pyrin/marenostrin protein, mainly expressed in neutrophils, activated monocytes and fibroblasts (Centola et al., 2000). Mutations affecting the B30.2 domain disrupts its regulatory interaction with caspase-1, a component of NLRP3 inflammasome (Chae et al., 2006), which results in uncontrolled secretion of mature IL-1β and of inflammatory response. Thus, FMF is considered as a syndrome related to the dysregulation of IL-1β production (Jesus and Goldbach-Mansky, 2014). IL-1β, with other cytokines IL-6 and TNF-α, enhances the hepatic synthesis of SAA protein (Jensen and Whitehead, 1998) which high and sustained levels are involved in the development of AA-amyloidosis. In fact, the fibrils forming the AA amyloid deposits are derived from the cleavage of SAA protein (Grateau et al., 2005). Among the auto-inflammatory diseases, FMF is the most responsible for renal AA-amyloidosis, a harmful complication which often leads to renal failure requiring dialysis, and associated with poor prognosis (Obici and Merlini, 2012). This complication develops subsequent to clinical signs (phenotype 1) in most patients. For others, AA-amyloidosis is the first clinical sign (phenotype 2) (Ben-Zvi and Livneh, 2011). Its occurrence has been reported to be dependent on the ethnic origin of FMF patients and countries. In pre-colchicine era, renal AA-amyloidosis was largely reported among Turkish (67%) and Sephardic Jews FMF patients (26.5%), and at a lesser extent among Armenian and Arab patients (Said et al., 1992). Even now, FMF remains a leading cause in occurrence of AA-amyloidosis in Turkey (Tuglular et al., 2002; Yilmaz et al., 2013). In the North African countries, few data are available about the renal AA- amyloidosis secondary to FMF. Only one study reported on two families in Morocco (Hama et al., 2012). Here, we explore for the first time this relationship by characterizing the mutational *MEFV* profile associated with this complication in Algerian FMF patients.

2. Patients and methods

2.1. Patients

This study included 28 unrelated patients recruited between 2009 and 2014, at departments of Nephrology of University Hospitals in the central and west regions of Algeria. Twenty three of these patients developed FMF symptoms. The diagnosis was based on clinical findings of classical FMF symptoms such as, recurrent fever, recurrent abdominal pain, recurrent chest pain and joint involvement. The remaining patients were asymptomatic with renal amyloidosis of unknown etiology. After clinical investigations which excluded other etiologies of AA amyloidosis, these patients were assumed to have phenotype 2 of FMF. Referring physicians collected data including the demographic data, clinical manifestations (age of onset of disease, attack duration, fever, abdominal pain, arthritis, chest pain, erysipelas-like erythema and amyloidosis), detailed family history of FMF and treatment with colchicine.

A group of 20 FMF controls without renal amyloidosis were selected for this study, according to their age, clinical symptoms, disease duration and colchicine therapy. They were all evaluated for renal function and recruited at the same period from department of internal medicine of the same University Hospitals.

2.2. Amyloid diagnosis

AA amyloidosis was diagnosed by microscopic examination of renal biopsies, except for two patients whose AA deposits were evidenced in salivary glands. The diagnosis of amyloidosis was based on a Congo-red staining of tissue sections. The type of amyloid deposits was provided by a potassium permanganate reaction according to Wright's method (Wright et al., 1977).

2.3. Genetic analysis

Genomic DNA was extracted from peripheral leukocytes using a standard protocol (Miller et al., 1988). Mutation detection in *MEFV* gene was performed by sequencing the entire coding sequence of exon 10 in forward and reverse directions after PCR amplification, according to the experimental protocol of Qatar Biomedical Research Institute (QBRI). PCR products were purified and the sequencing was performed by BigDye terminator chemistry on an ABI Genetic Analyser (3730xl). Sequences were analyzed by SeqScape 2.5 software (Applied Biosystems, Foster City, CA, USA).

2.4. Statistical analysis

The proportions comparison with continuity correction was carried out using the XL-STAT software (Version 18.06) for the small samples. The comparison between the quantitative variables (mean ± SD) was made by T-test for independent samples using Statistica software (Version 8). A double tailed p-value <0.05 was considered statistically significant.

2.5. Ethical considerations

This study was approved by the ethics committee and deontology of University of Sciences and Technology Houari Boumediene (USTHB, Algiers) which uses the standards and recommendations of the Declaration of Helsinki, and all patients or their legal guardians were consenting.

3. Results

This study included a group of patients with AA-amyloidosis (15 males and13 females, mean age: 39.70 ± 13.19 years) and a group of FMF controls (9 males and 11 females; mean age: 33.80 ± 14.71years) ($p = 0{,}189$). The age of onset of the attacks was comparable between the patients with (10.56 ± 5.93 years) and without amyloidosis (11.37 ± 8.69 years) ($p = 0.759$). The mean disease duration was 29.81 ± 14.62 years and 24.27 ± 11.43 years ($p = 0.225$), for the first and the second group of patients, respectively.

Out of the expected 56 mutant alleles, the genetic analysis identified 49 (87.5%) present in 27 patients with renal complication (Table 1). All these patients carried at least one mutation at codon 694 of *MEFV* gene, where p.M694I was the commonest (35/49 of identified mutant alleles, 71.4%). The p.M694V, p.M680I and p.I692Del mutations were identified at a lesser frequency, as shown in Table 1.

Out of the expected 40 mutant alleles, the genetic analysis in the controls identified 32 (80%), where p.M694I was predominant but with significantly lower frequency (16/40; 40%) compared to patients with amyloidosis ($p = 0.029$), followed by p.M694V (20%), p.M680I (15%) and p.A744S (5%) (all $p > 0.05$).

In patients with amyloidosis, seven different genotypes were observed with different proportions (Fig. 1). The M694I/M694I genotype was predominant (14/27; 52%) and was significantly associated with amyloidosis development compared to FMF controls (3/20; 15%) ($p = 0.022$). The M694V/M694V genotype was found in 3/27 (11%) patients, but its association with renal amyloidosis did not reach statistical significance compared to controls (0/20; 0%) ($p = 0.349$). The proportion of compound heterozygous genotypes was found with similar frequencies between the two groups of patients (5/27; 18.51% vs 9/20; 45%) ($p = 0.101$). The number of heterozygous patients did not differ between the

Table 1
Allele number and frequency of identified MEFV mutations in patients with amyloidosis.

Mutations	Homozygous	Heterozygous	Allele number (n)	Allele frequency (n = 56), %
p.M694I	14	7	35	62.5
p.M694V	3	4	10	17.86
p.M680I	0	3	3	5.36
p.I692Del	0	1	1	1.79
unidentified alleles			7	12.50
Total	17	15	56	100

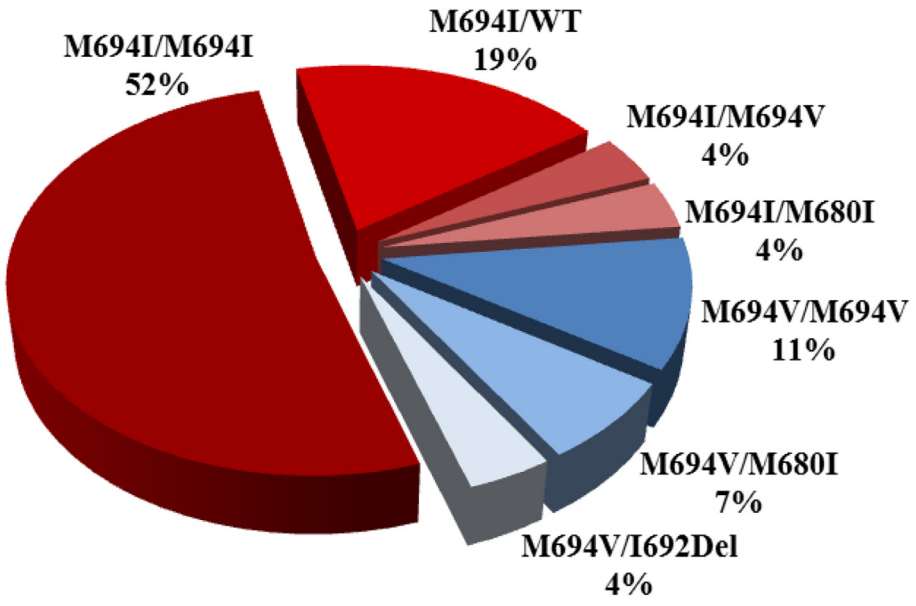

Fig. 1. Genotypes distribution in Algerian FMF patients with renal AA-amyloidosis.

two groups (5/27; 18.51% vs 8/20; 40%) ($p = 0.194$). One patient with renal amyloidosis did not have any mutation in exon 10 but he had a positive family history of FMF.

Out of the 5 patients with assumed phenotype 2, four were homozygous for p.M694I and one was heterozygous for the same mutation. The genotypes of the two patients in whom amyloidosis was evidenced in salivary glands were M694I/M694I and M694I/WT. The genotyping and clinical data are summarized in Table 2. Renal AA-amyloidosis was diagnosed at different stages in the analyzed patients. Fourteen developed end-stage renal disease (ESRD) of whom 6 (42.8%) died (Table 2). One of those who died has never received colchicine and was homozygous for p.M694I mutation. None of the patients started colchicine treatment prior to AA-amyloidosis development. In these patients, not only amyloidosis was diagnosed at a late age (35.42 ± 14.57 years) but also, colchicine prophylaxis was delayed as time between FMF onset and amyloidosis confirmation was long (26.5 ± 15.66 years). The same situation was encountered in our controls where 40% of them started colchicine therapy very late, 13–26 years after FMF onset and others were never treated two of whom were M694I/M694I.

4. Discussion

This study focused on *MEFV* gene mutations in patients with secondary AA amyloidosis, which can lead to end-stage renal disease (ESRD) and death (Shohat et al., 1999). The analyzed patients did not receive colchicine until biopsy-proven amyloidosis. In 50% of patients, the biopsy was undertaken too late, coinciding with ESRD. This may explain the ineffectiveness of colchicine therapy and the death of 6 (42.8%) patients with ESRD during the study period. Before the colchicine era, renal complication was fatal and responsible for 67% of deaths (Shohat et al., 1999). A recent study showed that ESRD remains the leading cause of death in FMF patients, in 35% and 60% of men and women, respectively (Twig et al., 2014). In our cohort, FMF was not diagnosed before the development of renal AA-amyloidosis. Indeed, in Algeria, FMF is underdiagnosed which may lead to an under-estimate of the incidence of secondary AA-amyloidosis.

In this study, mutation analysis revealed a predominance of p.M694I in both groups of FMF patients, as previously reported (Ait-Idir et al., 2011). With regard to amyloidosis, we showed a significant association between this mutation at homozygous state and the renal complication. This result suggests that the M694I/M694I genotype may be a genetic risk factor for the occurrence of renal AA-amyloidosis in Algerian FMF patients. Here, we identified for the first time the M694V/M694V genotype among our FMF patients, but failed to demonstrate its association with the development of amyloidosis. Even in our previous study, one of the two patients with this complication was homozygous for p.M694I (Ait-Idir et al., 2011). Also, it is important to note that in the five patients with the phenotype 2, four were homozygous for p.M694I. A predominance of genetic variations affecting the 694 codon of *MEFV* gene has been previously reported in Arab patients with renal amyloidosis, but with a high homozygous proportion of p.M694V compared to p.M694I (Ben-Chetrit and Backenroth, 2001; Mansour et al., 2001). The homozygosity for p.M694V was reported as the main genetic risk factor for the occurrence of AA-amyloidosis in both phenotypes 1 and 2 of FMF. Indeed, several studies

Table 2
Genotypes and clinical features of the 28 patients with renal AA-amyloidosis.

Patients (n = 28)	Sex	*MEFV* Genotype	Clinical manifestations				Age at diagnosis (years)	Amyloidosis course
			Fever	Abdominal pains	Articular pains	Thoracic pains		
1	M	M694I/M694I	+	+	+	+	19	Dialysis
2	F	M694I/M694I	+	+	+	+	30	CRF
3	F	M694I/M694I	+	+	+	–	30	Dialysis
4	M	M694I/M694I	+	+	–	–	55	Dialysis
5	F	M694I/M694I	+	+	+	–	28	Nephrotic syndrome
6	M	M694I/M694I	+	+	+	–	31	Dialysis, deceased
7	F	M694I/M694I	+	+	+	–	24	Nephrotic syndrome
8	F	M694I/M694I	+	+	–	–	33	Dialysis
9	M	M694I/M694I	+	+	+	–	24	Dialysis
10	M	M694I/M694I	+	+	+	–	44	Nephrotic syndrome
11	F	M694I/M694I	Asymptomatic				NA	NA
12	M	M694I/M694I	Asymptomatic				52	Nephrotic syndrome
13	F	M694I/M694I	Asymptomatic				41	Dialysis, deceased
14	F	M694I/M694I	Asymptomatic				27	Dialysis
15	M	M694V/M694V	–	+	+	–	NA	Dialysis
16	M	M694V/M694V	+	+	+	–	48	CRF
17	M	M694V/M694V	+	+	–	–	23	Dialysis, deceased
18	M	M694I/M694V	–	+	–	–	16	CRF
19	F	M694V/M680I	+	+	–	–	55	Proteinuria
20	F	M694V/M680I	+	+	+	–	53	Dialysis, deceased
21	F	M694I/M680I	+	+	–	–	53	Dialysis, deceased
22	M	M694V/I692Del	+	+	–	–	40	Nephrotic syndrome
23	M	M694I/WT	+	+	+	–	38	CRF
24	F	M694I/WT	+	+	–	–	13	CRF
25	M	M694I/WT	+	+	+	–	59	CRF
26	F	M694I/WT	+	+	+	–	50	Proteinuria
27	M	M694I/WT	Asymptomatic				30	Dialysis
28	M	WT/WT	+	+	+	–	8	Dialysis, deceased

(NA: data not available; CRF: Chronic renal failure; WT: wild type).

demonstrated a significant correlation between this complication and M694V/M694V among Non-Ashkenazi Jewish, Turkish, Arab and Armenian patients (Altunoğlu et al., 2013; Balci et al., 2002; Livneh et al., 1999; Mimouni et al., 2000). Moreover, this risk was enhanced by 6 fold with the M694V/M694V genotype in Turkish patients (Kasifoglu et al., 2014). Nevertheless, other studies did not support this relationship (Atagunduz et al., 2004; Mukhin et al., 2015). Touitou et al. have demonstrated formally that the country of recruitment is the main risk factor for the development of renal amyloidosis secondary to FMF (Touitou et al., 2007). A more recent meta-analysis confirmed the environmental impact on the expression of FMF between the children living in eastern Mediterranean and western European countries (Ozen et al., 2014).

According to our results, the occurrence of AA-amyloidosis in asymptomatic patients with the p.M694I mutation, suggests a more severe phenotype associated with this variant in Algerians than in Arabs, despite the fact that it has been previously related to mild phenotype in Arab patients (Majeed et al., 2002). Since it affects the B30.2 domain of pyrin protein, p.M694I was associated with a severe phenotype of FMF (Weinert et al., 2009), which may explain its association with the occurrence of renal AA-amyloidosis. In fact, the B30.2 domain was implicated in the negative role of wild pyrin in the IL-1β synthesis pathway (Chae et al., 2006). A computing model revealed that p.M694V and p.M680I mutations altered the interaction between the B.30 domain and caspase-1. However, the effect of p.M694V mutation was stronger than that of p.M680I mutation, which is compatible with clinical effects caused by these mutations (Arakelov et al., 2015). Among our patients with amyloidosis, less frequent genotypes were identified where p.M694I and p.M694V were in combination with p.M680I and I692Del. In contrast to previous data, we report for the first time the M694I/M680I and M694V/I692Del genotypes in Maghrebian patients with AA-amyloidosis (Dodé et al., 2002). However, the risk of renal complication was not associated with any of these genotypes. Among the patients with amyloidosis, five carried a single p.M694I allele and one was free from *MEFV* mutations, but the presence of another mutation in another *MEFV* exon is not excluded. This study will be continued to include a larger number of patients with and without renal complication and by investigating the SAA-1 gene polymorphism which has been recognized as a genetic modifier influencing the development of renal AA-amyloidosis (Cazeneuve et al., 2000; Delibas et al., 2005).

5. Conclusion

This is the first study reporting the genotype-phenotype correlation pattern related to renal AA-amyloidosis in Algerian FMF patients. The present results clearly show an association between homozygosity for p.M694I mutation and renal AA amyloidosis in FMF patients with and without clinical symptoms. These results point on the importance of an earlier diagnosis and treatment of FMF in attempt to decrease the incidence of renal AA-amyloidosis in Algerian patients suffering from FMF.

Conflict of interest

No conflict of interest to declare.

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References

Ait-Idir, D., Khilan, A., Djerdjouri, B., El-Shanti, H., 2011. Spectrum of mutations and carrier frequency of familial Mediterranean fever gene in the Algerian population. Rheumatology 50, 2306–2310.
Altunoğlu, A., Erten, Ş., Canoz, M.B., Yuksel, A., Ceylan, G.G., Balci, S., Dogan, H.T.,

2013. Phenotype 2 familial Mediterranean fever: evaluation of 22 case series and review of the literature on phenotype 2 FMF. Ren. Fail 35, 226–230.
Arakelov, G.G., Osipov, O.V., Nazaryana, K.B., 2015. Effects of M680I and M694V pyrin mutations on the tertiary structure of domain B30.2 and its interaction with caspase-1: in silico analysis. Mol. Biol. 49, 736–741.
Atagunduz, M.P., Tuglular, S., Kantarci, G., Akoglu, E., Direskeneli, H., 2004. Association of FMF-related (MEFV) point mutations with secondary and FMF amyloidosis. Nephron Clin. Pract. 96, c131–c135.
Balci, B., Tinaztepe, K., Yilmaz, E., Guçer, Ş., Ozen, S., Topaloğlu, R., Beşbaş, N., Ozguç, M., Bakkaloğlu, A., 2002. MEFV gene mutations in familial Mediterranean fever phenotype II patients with renal amyloidosis in childhood: a retrospective clinicopathological and molecular study. Nephrol. Dial. Transpl. 17, 1921–1923.
Ben-Chetrit, E., Backenroth, R., 2001. Amyloidosis induced, end stage renal disease in patients with familial Mediterranean fever is highly associated with point mutations in the MEFV gene. Ann. Rheum. Dis. 60, 146–149.
Ben-Chetrit, E., Levy, M., 1998. Familial Mediterraneanfever. Lancet 351, 659–664.
Ben-Chetrit, E., Touitou, I., 2009. Familial Mediterranean fever in the world. Arthritis Rheum. 61, 1447–1453.
Ben-Zvi, I., Livneh, A., 2011. Chronic inflammation in FMF: markers, risk factors, outcomes and therapy. Nat. Rev. Rheumatol. 7, 105–112.
Cazeneuve, C., Ajrapetyan, H., Papin, S., Roudot-Thoraval, F., Geneviève, D., Mndjoyan, E., Papazian, M., Sarkisian, A., Babloyan, A., Boissier, B., Duquesnoy, P., Kouyoumdjian, J.-C., Girodon-Boulandet, E., Grateau, G., Sarkisian, T., Amselem, S., 2000. Identification of MEFV-independent Modifying genetic factors for familial Mediterranean fever. Am. J. Hum. Genet. 67, 1136–1143.
Centola, M., Wood, G., Frucht, D.M., Galon, J., Aringer, M., Farrell, C., Kingma, D.W., Horwitz, M.E., Mansfield, E., Holland, S.M., O'Shea, J.J., Rosenberg, H.F., Malech, H.L., Kastner, D.L., 2000. The gene for familial Mediterranean fever, MEFV, is expressed in early leukocyte development and is regulated in response to inflammatory mediators. Blood 95, 3223–3231.
Chae, J.J., Wood, G., Masters, S.L., Richard, K., Park, G., Smith, B.J., Kastner, D.L., 2006. The B30.2 domain of pyrin, the familial Mediterranean fever protein, interacts directly with caspase-1 to modulate IL-1 production. Proc. Natl. Acad. Sci. U. S. A. 103, 9982–9987.
Delibas, A., Öner, A., Balci, B., Demircin, G., Bülbül, M., Bek, K., Erdoğan, Ö., Baysun, S., Yilmaz, E., 2005. Genetic risk factors of amyloidogenesis in familial Mediterranean fever. Am. J. Nephrol. 25, 434–440.
Dodé, C., Hazenberg, B.P., Pêcheux, C., Cattan, D., Moulin, B., Barthélémy, A., Gubler, M.C., Delpech, M., Grateau, G., 2002. Mutational spectrum in the MEFV and TNFRSF1A genes in patients suffering from AA amyloidosis and recurrent inflammatory attacks. Nephrol. Dial. Transpl. 17, 1212–1217.
El-Shanti, H., Majeed, H.A., El-Khateeb, M., 2006. Familial Mediterranean fever in Arabs. Lancet 367, 1016–1024.
French FMF Consortium, 1997. A candidate gene for familial Mediterranean fever. Nat. Genet. 17, 25–31.
Grateau, G., Jéru, I., Rouaghe, S., Cazeneuve, C., Ravet, N., Duquesnoy, P., Cuisset, L., Dodé, C., Delpech, M., Amselem, S., 2005. Amyloidosis and auto-inflammatory syndromes. Curr. Drug Targets - Inflamm. Allerg. 4, 57–65.
Hama, I., Ilham, R., Ouzeddoun, N., Alhamany, Z., Bayahia, R., Sefiani, A., 2012. Renal amyloidosis due to familial Mediterranean fever misdiagnosed. Indian J. Hum. Genet. 18, 363–365.
Jensen, L.E., Whitehead, A.S., 1998. Regulation of serum amyloid A protein expression during the acute-phase response. Biochem. J. 334, 489–503.
Jesus, A.A., Goldbach-Mansky, R., 2014. IL-1 blockade in autoinflammatory syndromes. Annu. Rev. Med. 65, 223–244.
Kasifoglu, T., Bilge, S.Y., Sari, I., Solmaz, D., Senel, S., Emmungil, H., Kilic, L., Oner, S.Y., Yildiz, F., Yilmaz, S., Bakirli, D.E., Tufan, M.A., Yilmaz, S., Yazisiz, V., Pehlivan, Y., Bes, C., Cetin, G.Y., Erten, S., Gonullu, E., Temel, T., Sahin, F., Akar, S., Aksu, K., Kalyoncu, U., Direskeneli, H., Erken, E., Kisacik, B., Sayarlioglu, M., Korkmaz, C., 2014. Amyloidosis and its related factors in Turkish patients with familial Mediterranean fever: a multicentre study. Rheumatology 53, 741–745.
Livneh, A., Langevitz, P., Shinar, Y., Zaks, N., Kastner, D.L., Pras, M., Pras, E., 1999. MEFV mutation analysis in patients suffering from amyloidosis of familial Mediterranean fever. Amyloid 6, 1–6.
Majeed, H.A., El-Shanti, H., Al-Khateeb, M.S., Rabaiha, Z.A., 2002. Genotype/phenotype correlations in Arab patients with familial Mediterranean fever. Semin. Arthritis Rheum. 31, 371–376.
Mansour, I., Delague, V., Cazeneuve, C., Dodé, C., Chouery, E., Pêcheux, C., Medlej-Hashim, M., Salem, N., Zein, L.E., Levan-Petit, I., Lefranc, G., Goossens, M., Delpech, M., Amselem, S., Loiselet, J., Grateau, G., Mégarbane, A., Naman, R., 2001. Familial Mediterranean fever in Lebanon: mutation spectrum, evidence for cases in Maronites, Greek orthodoxes, Greek catholics, Syriacs and Chiites and for an association between amyloidosis and M694V and M694I mutations. Eur. J. Hum. Genet. 9, 51–55.
Miller, S.A., Dykes, D.D., Polesky, H.F., 1988. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res. 16, 1215.
Mimouni, A., Magal, N., Stoffman, N., Shohat, T., Minasian, A., Krasnov, M., Halpern, G.J., Rotter, J.I., Fischel-Ghodsian, N., Danon, Y.L., Shohat, M., 2000. Familial Mediterranean fever: effects of genotype and ethnicity on inflammatory attacks and amyloidosis. Pediatrics 105, E70.
Mukhin, N.A., Kozlovskaya, L.V., Bogdanova, M.V., Rameev, V.V., Moiseev, S.V., Simonyan, A.K., 2015. Predictors of AA amyloidosis in familial Mediterranean fever. Rheumatol. Int. 35, 1257–1261.
Obici, L., Merlini, G., 2012. Amyloidosis in autoinflammatory syndromes. Autoimmun. Rev. 12, 14–17.
Ozen, S., Demirkaya, E., Amaryan, G., Koné-Paut, I., Polat, A., Woo, P., Uziel, Y., Modesto, C., Finetti, M., Quartier, P., Papadopoulou-Alataki, E., Al-Mayouf, S.M., Fabio, G., Gallizzi, R., Cantarini, L., Frenkel, J., Nielsen, S., Hofer, M., Insalaco, A., Acikel, C., Ozdogan, H., Martini, A., Ruperto, N., Gattorno, M., Project, f.t.P.R.I.-T.O.P.a.t.E, 2014. Results from a multicentre international registry of familial Mediterranean fever: impact of environment on the expression of a monogenic disease in children. Ann. Rheum. Dis. 73, 662–667.
Said, R., Hamzeh, Y., Said, S., Tarawneh, M., Al-Khateeb, M., 1992. Spectrum of renal involvement in familial Mediterranean fever. Kidney Int. 41, 414–419.
Shohat, M., Halpern, G.J., 2011. Familial Mediterranean fever- A review. Genet. Med. 13, 487–498.
Shohat, M., Magal, N., Shohat, T., Chen, X., Dagan, T., Mimouni, A., Danon, Y., Lotan, R., Ogur, G., Sirin, A., Schlezinger, M., Halpern, G.J., Schwabe, A., Kastner, D., Rotter, J.I., Fischel-Ghodsian, N., 1999. Phenotype-genotype correlation in familial Mediterranean fever: evidence for an association between Met694Val and amyloidosis. Eur. J. Hum. Genet. 7, 287–292.
The International FMF Consortium, 1997. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. Cell 90, 797–807.
Touitou, I., Sarkisian, T., Medlej-Hashim, M., Tunca, M., Livneh, A., Cattan, D., Yalçinkaya, F., Özen, S., Majeed, H., Ozdogan, H., Kastner, D., Booth, D., Ben-Chetrit, E., Pugnère, D., Michelon, C., Séguret, F., Gershoni-Baruch, R., Fever, I.S.G.f.P.-G.C.i.F.M, 2007. Country as the primary risk factor for renal amyloidosis in familial Mediterranean fever. Arthritis Rheum. 56, 1706–1712.
Tuglular, S., Yalcinkaya, F., Paydas, S., Oner, A., Utas, C., Bozfakioglu, S., Ataman, R., Akpolat, T., Ok, E., Sen, S., Düsünsel, R., Evrenkaya, R., Akoglu, E., 2002. A retrospective analysis for aetiology and clinical findings of 287 secondary amyloidosis cases in Turkey. Nephrol. Dial. Transpl. 17, 2003–2005.
Twig, G., Livneh, A., Vivante, A., Afek, A., Shamiss, A., Derazne, E., Tzur, D., Ben-Zvi, I., Tirosh, A., Barchana, M., Shohat, T., Golan, E., Amital, H., 2014. Mortality risk factors associated with familial Mediterranean fever among a cohort of 1.25 million adolescents. Ann. Rheum. Dis. 73, 704–709.
Weinert, C., Grütter, C., Roschitzki-Voser, H., Mittl, P.R.E., Grütter, M.G., 2009. The crystal structure of human pyrin B30.2 domain: implications for mutations associated with familial Mediterranean fever. J. Mol. Biol. 394, 226–236.
Wright, J., Calkins, E., Humphrey, R., 1977. Potassium permanganate reaction in amyloidosis. A histologic method to assist in differentiating forms of this disease. Lab. Invest. 36, 274–281.
Yilmaz, M., Unsal, A., Sokmen, M., Kaptanogullari, O.H., Alkim, C., Kabukcuoglu, F., Ozagari, A., Bor, E., 2013. Renal involvement in AA amyloidosis: clinical outcomes and survival. Kidney Blood Press Res. 37, 33–42.